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Cannabinoids in Clinical Practice

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Abstract

Cannabis has a potential for clinical use often obscured by unreliable and purely anecdotal reports. The most important natural cannabinoid is the psychoactive tetrahydrocannabinol (Δ^9-THC); others include cannabidiol (CBD) and cannabigerol (CBG). Not all the observed effects can be ascribed to THC, and the other constituents may also modulate its action; for example CBD reduces anxiety induced by THC. A standardised extract of the herb may be therefore be more beneficial in practice and clinical trial protocols have been drawn up to assess this. The mechanism of action is still not fully understood, although cannabinoid receptors have been cloned and natural ligands identified.

Cannabis is frequently used by patients with multiple sclerosis (MS) for muscle spasm and pain, and in an experimental model of MS low doses of cannabinoids alleviated tremor. Most of the controlled studies have been carried out with THC

rather than cannabis herb and so do not mimic the usual clincal situation. Small clinical studies have confirmed the usefulness of THC as an analgesic; CBD and CBG also have analgesic and antiinflammatory effects, indicating that there is scope for developing drugs which do not have the psychoactive properties of THC. Patients taking the synthetic derivative nabilone for neurogenic pain actually preferred cannabis herb and reported that it relieved not only pain but the associated depression and anxiety. Cannabinoids are effective in chemotherapy-induced emesis and nabilone has been licensed for this use for several years. Currently, the synthetic cannabinoid HU211 is undergoing trials as a protective agent after brain trauma. Anecdotal reports of cannabis use include case studies in migraine and Tourette's syndrome, and as a treatment for asthma and glaucoma.

Apart from the smoking aspect, the safety profile of cannabis is fairly good. However, adverse reactions include panic or anxiety attacks, which are worse in the elderly and in women, and less likely in children. Although psychosis has been cited as a consequence of cannabis use, an examination of psychiatric hospital admissions found no evidence of this, however, it may exacerbate existing symptoms. The relatively slow elimination from the body of the cannabinoids has safety implications for cognitive tasks, especially driving and operating machinery; although driving impairment with cannabis is only moderate, there is a significant interaction with alcohol.

Natural materials are highly variable and multiple components need to be standardised to ensure reproducible effects. Pure natural and synthetic compounds do not have these disadvantages but may not have the overall therapeutic effect of the herb.

Cannabis has a long medical history which has been well reviewed, ranging from its anecdotal use in ancient times, through medical prescribing in the 19th and early 20th centuries to modern, usually illicit, self-medication.[1-6] Cannabis and the cannabinoids have been suggested as therapeutic agents in so many conditions that there is some danger of them being viewed as panaceas. Problems inherent in their use centre on the legal position of cannabis as a proscribed drug (and the accompanying stigma), which applies in most parts of the world, and because the most common route of delivery is by smoking (which is unacceptable) together with the unreliability of crude cannabis. The legal classification in most countries is based on the premise that cannabis has no demonstrable therapeutic benefit (although the pure isolated cannabinoid dronabinol and the semi-synthetic nabilone are licensed for clinical use) which has rather limited the opportunities for proper clinical assessment. The anecdotal evidence regarding clinical efficacy is difficult to evaluate because many users are reluctant to admit to it, and good clinical trial information is actually fairly rare. In this review, the use of cannabis in practice, isolated natural and synthetically modified cannabinoids, their adverse effects and future potential will be addressed.

1. Overview of Cannabinoid Chemistry and Pharmacology

1.1 Constituents of Cannabis

The major active constituents of the plant *Cannabis sativa* are the cannabinoids, which are substituted meroterpenes[1-3] and not alkaloids, as is often erroneously stated. About 70 naturally occurring cannabinoids are known today but of these, the most important psychoactive compound is considered to be tetrahydrocannabinol, or THC, and its most active isomer the Δ^9 form (previously referred to as Δ^1 THC). Other isomers occur, such as the Δ^8 isomer (previously Δ^6 THC), which is present in

very low concentrations and is less potent psychotropically.[2] Various derivatives have also been made; of these, nabilone is commercially available and licensed for the alleviation of cancer chemotherapy-induced emesis (CIE). Δ^9 THC itself has been synthesised and marketed as dronabinol, also for CIE. The other most important compounds are cannabidiol (CBD), cannabigerol (CBG), cannabinol (CBN; an oxidation product of THC and an indication that the herb has deteriorated), cannabichromene (CBC), and olivetol, their biosynthetic precursor. In the herb these occur together with their corresponding carboxylic acid derivatives, e.g. THC acid, which represents a complication with some dosage forms since their pharmacokinetic properties are very different. Cannabis herb also contains many other compounds such as flavonoids, which may or may not contribute to the biological activity of the herb. Information on new synthetic cannabinoids with therapeutic potential is limited for commercial reasons, but one such is dexanabinol (HU-211), a nonpsychoactive cannabinoid with pronounced antiemetic activity and a protective effect on the blood brain barrier, which is now undergoing clinical assessment.[2]

1.2 Cannabis Herb or Isolated Cannabinoids?

Pharmacological evidence in animal models suggests that not all the observed therapeutic affects of the cannabis herb can be ascribed to the THC content or indeed any single cannabinoid. Even back in 1974, a human study involving experienced users of cannabis showed that individuals could not always detect high concentrations of THC in their cigarettes and claimed in some cases that cannabis with low concentrations of THC was satisfactory, when the samples had a high CBD content.[7] A recent small clinical trial in 12 regular users of cannabis has shown subtle subjective differences in the effect of THC alone when compared with the herb, in that euphoria was generally greater in the THC group and sedation was more marked in the group given the herb.[8] In these studies the objective assessed was euphoria, which is obviously a different matter to a required medicinal effect, but it illustrates the fact that not all the pharmacological effects of cannabis herb reside in the THC content. The other constituents are known to have different pharmacological activities, not always psychotropic, and may also modulate the action of THC.[9] For example, CBD, which is not psychotropic in itself, has been demonstrated to be anxiolytic in animals and humans and to reduce the anxiety reaction induced by THC.[10] CBD also elevates THC levels, and those of other drugs, in the brain of the mouse.[11]

Therefore, it is possible that a standardised extract of the herb, containing known amounts of THC and CBD, and possibly some of the other components, may be more beneficial in practice than a single compound. This would require more information about the other constituents but would fit well with the anecdotal evidence which almost exclusively concerns the herb. Recently, clinical trial protocols have been drawn up to assess further whether the clinical efficacy of the herb, standardised to THC content, is similar to the effect obtained by THC alone.[12] The matter is complicated by the fact that the time course and bioavailability of the cannabinoids taken by the routes of smoking and by oral administration are obviously very different and not well known. Clinical trials carried out on the herb are unreliable if the extract has not been assayed for active constituents and this is a major disadvantage of much of the work previously carried out. In addition, isolated cases of problems due to microbial contamination have been observed, for example a case of allergic bronchopulmonary aspergillosis due to mouldy cannabis herb has been reported[13] and it is likely that there are more such cases which have not been publicised because of the illegal nature of the herb.

1.3 Pharmacology of Cannabinoids

1.3.1 Tetrahydrocannabinol, Anandamide and the Endocannabinoids

The full mechanism of action of the cannabinoids and the role of the endocannabinoid system is still poorly understood. Although behavioural and

neuropharmacological effects of THC were investigated throughout the 1970s and 1980s, it was only in 1990 that a receptor for THC in the CNS was cloned (now known as the CB1 receptor)[14] and in 1992 a major natural ligand of THC was identified and named anandamide.[15] Another cannabinoid receptor was cloned from macrophages and the spleen in 1993, and is now termed the peripheral or CB2 receptor.[16] Anandamide is the ethanolamide of arachidonic acid,[15] and a series of endogenous analogues have now been isolated which are all able to bind in a similar way to the CB1 receptor and are termed 'anandamides'. A series of naturally-occurring fatty acid monoglycerides have also been identified, the most important being 2-arachidonoylglycerol (2-Ara-Gl), which acts in the same way as anandamide. Interestingly, related glycerides such as 2-linoleoylglycerol and 2-palmitoyl glycerol do not bind to the CB1 receptor, but act as potentiators for the binding of 2-Ara-Gl. A mixture of all three is also more potent in some systems and is termed the 'entourage' effect which is a form of synergy.[2,17] Some fatty acid amides, which do not themselves bind to CB1 receptors, nevertheless show *in vivo* cannabimimetic activity, which is thought to be due to inhibition of anandamide metabolism. This is thought to be the mechanism by which the 'sleep lipid', oleamide has its effect.[18] The endocannabinoids are released by macrophages during haemorrhagic shock, resulting in a rapid decrease in blood pressure which has led to the suggestion that anandamide is actually the endothelin-derived hyperpolarising factor (EDHF) which may be one of the regulators of blood pressure.[19] Recent work has indicated that 2-Ara-Gl may also play a role in the cardiovascular system.[2]

This then is the molecular basis for most of the activity of THC, but there are also instances where anandamide and THC do not have identical effects, and for example, very low doses of anandamide actually inhibit the effects of THC.[20] These discrepancies are not surprising given the chemical structural differences between them and the complex nature of anandamide pharmacology. The theory also does not take into account other observed effects such as stimulation of the release of opioid peptides involved in pain control[2] and the action of the other cannabinoids. For reviews of the endocannabinoid system, see references.[21,22]

1.3.2 The Others: Cannabidiol, Cannabigerol, Cannabinol and Olivetol

CBD is the other important natural cannabinoid, and in fact one of the few others which has been investigated pharmacologically. It has a modulating effect on brain THC levels,[11] but also has intrinsic activity itself. Although not psychoactive it has a potent analgesic and anti-inflammatory effect mediated by a dual cyclooxygenase and lipoxygenase inhibition. This anti-inflammatory effect is several hundred times that of aspirin (acetysalicylic acid) when measured in standard animal tests and isolated cell assays.[23] However, after oral administration it appears to act mainly as a lipoxygenase inhibitor.[1,23] CBD, like THC and CBN, also stimulates the release of prostaglandin (PG)E_2 from synovial cells and, like THC, inhibits leukotriene B_4 synthesis in human polymorphonuclear cells *in vitro*.[24] Of the other cannabinoids, CBN has a centrally acting effect like THC (but much less potent), CBG is a lipoxygenase inhibitor without cyclooxygenase activity, and olivetol inhibits cycloxygenase with no effect on lipoxygenase.[23] Therefore, there is potential for developing analgesic drugs based on these cannabinoids which do not have the psychoactive properties of THC.

2. Therapeutic Applications of Cannabinoids

Probably the most important applications for cannabinoids at present tend to be diseases where the existing treatments are not wholly satisfactory, for example, neurological conditions like multiple sclerosis (MS), and chronic intractable pain and drug-induced emesis. There may be a place for cannabinoids in glaucoma, asthma and cardiovascular conditions, although clinical use in these indications is some way in the future. The possibility of using cannabinoids in psychiatric illness is more complex since it is often assumed that cannabis is more likely to cause rather than alleviate psychiatric

disorders. The evidence and theories which have been advanced to support this use are discussed in section 2.1.6.

2.1 Neurological Disorders

2.1.1 Multiple Sclerosis and Muscle Spasticity

The British Medical Association has concluded that: 'cannabinoids may have a potential use for patients with spastic neurological disorders such as MS and spinal cord injury. Such patients often have distressing symptoms which are not well controlled with available drugs. Carefully controlled trials of cannabinoids in patients which have not responded to other drugs are indicated'.[25]

MS is progressive in nature, and characterised by muscle spasticity, pain, tremor, balance problems, fatigue and incontinence. Cannabis is estimated to be taken by over 1% of patients with MS,[2] mainly for muscle spasm and the pain associated with it. In an experimental animal model of MS, low doses of cannabinoids alleviated tremor,[26] and patients with MS have indeed found that tremor is reduced.[27] Patients with spasticity have also benefitted from the administration of THC at a dose of around 7.5mg.[28,29] Other MS-related symptoms have improved after taking cannabis. A trial of 112 patients who smoked cannabis found that over 90% experienced relief of chronic pain, and over 70% reported relief of trigeminal neuralgia associated with MS.[30]

The fact that certain other symptoms were not improved suggests that it is not a placebo effect, otherwise one would expect all symptoms to be affected equally. However, in general, much of the evidence is anecdotal. A recent case study on a patient with pendular nystagmus (disabling spasms of the eye muscles) showed a dramatic improvement after smoking cannabis.[31] This was important as the spasms could be monitored with an oscilloscope and related to the levels of cannabinoids in the blood, thus eliminating subjectivity. Other clinical trials support these reports to some extent.

Unfortunately most controlled studies have been carried out with THC rather than cannabis herb,[1,32] with the disadvantage that the modifying effect of CBD was absent.[33] One study used nabilone, which is licensed for anti-emetic use, for the dystonia associated with MS, and it did help significantly.[34] A study of 10 patients who smoked cannabis found that it negatively affected balance when assessed by electronic equipment and videotaping, but not when a standard neurological assessment was used.[35] Other studies involved small numbers of patients and were somewhat equivocal.[2,33,36] A more reasoned approach, focussing on mixtures of cannabinoids perhaps, could probably maximise benefit and minimise psychoactive adverse effects.

2.1.2 Movement Disorders and Parkinson's Disease

There are other dystonias, unrelated to MS, which have responded to cannabinoids. In 2 small studies, CBD was found to be moderately effective in controlling dystonic movement disorders[37,38] and Meige's syndrome.[39] These studies do not mimic the usual situation in real life, where patients may be smoking cannabis, but have the advantage that CBD lacks central activity and smoking is avoided. The therapeutic potential in other forms of dystonia is less clear because, in patients with Huntington's disease, nabilone actually increased choreatic movements.[40] In patients with Parkinson's disease, cannabis in the form of a cigarette (1g of cannabis containing 2.9% THC) was shown to have little effect on tremor in the small study carried out,[41] although there are good theoretical reasons why certain types of CB1 receptor agonists may find an application here. The whole area of brain cannabinoid systems as targets for therapy of neurological disorders has been well reviewed by Consroe.[22]

2.1.3 Pain Relief

Cannabinoids would make useful analgesics if psychotropic adverse effects could be accommodated. Animal studies show that both THC and CBD have analgesic properties, although they act through different mechanisms.[1,3,5,6] Several small clinical studies have confirmed the usefulness of THC, which at doses of 15 to 20mg was found to be comparable to codeine 60 to 120mg.[42] A standardised

cannabis extract (capsules containing 5 or 10mg THC) taken orally was used in a patient with familial Mediterranean fever, resulting in a reduced demand for morphine compared with placebo.[43] Nabilone has also shown efficacy in the treatment of neurogenic pain and has been tested at a dose range of 0.25 to 10mg.[44] However, these studies do not mimic the anecdotal use, and there are problems of bioavailability with oral cannabis preparations.

Types of pain for which current treatment is unsatisfactory and for which cannabis has anecdotal support include phantom limb pain following amputation, and pain secondary to damaged nerves.[26] The anti-inflammatory effects of some cannabinoids (e.g. CBD),[45] would also suggest benefits for rheumatoid and other autoimmune diseases. There are a few case reports of people using cannabis for migraine,[46] however, although there is a rationale for their use, in that cannabinoids inhibit platelet aggregation,[47] there is a lack of clinical data. Perception of pain is subjective and there have been conflicting reports regarding analgesia[48] and even increased sensitivity to pain.[49,50] There is still ample evidence that cannabinoids are useful for pain of different types, apart from that caused by thermal or electrical stimuli, dental pain and some types of cancer pain.[48]

2.1.4 Head Injury

A synthetic cannabinoid dexabinol is undergoing clinical evaluation as a treatment for brain trauma and cerebral ischaemia. Dexabinol has no psychotropic activity but blocks N-methyl D-aspartate (NMDA) receptors and this is thought to be the mechanism by which it protects against further damage. CBD and THC have antioxidant activity which is more potent even than ascorbate and α-tocopherol, and have been found to reduce glutamate toxicity in rat cortical neuron cultures and reduce oxidative damage in several *in vitro* tests.[51] This means that both CB1 receptor agonists and non-CB1 agonists may affect the pathology of neurological diseases. Dexabinol suppresses production of tumour necrosis factor, blocks NMDA-induced tremor, convulsions and death in mice, and reduces some effects of head injury in rats, and improves the integrity of the blood brain barrier. Phase I trials have been carried out in volunteers with up to 100mg dexabinol, which have shown no undesirable CNS or other effects, and phase II trials in several Israeli hospitals in cases of CNS trauma resulted in a lowering of intracranial pressure and a generally more favourable outcome.[2]

2.1.5 Tourette's Syndrome

This chronic neurological condition starts in childhood and is characterised by motor and vocal tics. It is usually treated with haloperidol and a defect in the brain dopamine system is thought to be responsible, since dopamine agonists such as methylphenidate are known to exacerbate the condition. Cannabinoid receptor CB1 agonists can also activate dopamine neurons in the ventral tegmentum,[52] and from this and other evidence it seems that endocannabinoid pathways have much in common with those involved in the pathophysiology of Tourette's syndrome,[22] although the mechanism by which they may act is unknown.

In 1988, 3 patients reported relief of motor tics during cannabis smoking,[53] and in 1993 a patient reported continuous relief with long term cannabis smoking.[54] More recently, an improvement in vocal as well as motor tics has been shown, as assessed by interviews.[55,56] THC also been assessed in an open prospective study in a 25-year old man, where a dose of 10mg resulted in an improvement in both motor and vocal tics, and also cognitive functions as measured by neurophysiological tests.[57]

2.1.6 Neuroses and Psychoses

Depression is understandably an associated feature of many chronic illnesses, and improvement of the other symptoms of the disease may help to alleviate it. In 1 trial,[5] patients taking nabilone for neurogenic pain relief preferred cannabis for the pain and reported that it relieved the associated depression and anxiety more effectively than nabilone. As cannabidiol is probably the agent responsible for any anxiolytic effect of cannabis, this finding is not surprising.[1,2,10]

The evidence for cannabis as an antidepressant is conflicting. A review of the literature showed that

in 5 cases, cannabis appeared to have a direct antidepressant effect[58] but results from a study of psychiatric out-patients suggest that it may actually provoke anxiety attacks.[59] The amotivational syndrome observed in chronic users of cannabis is thought to be due to depression[60] but the fact that patients who are depressed may smoke cannabis does not prove either a causal or therapeutic effect.

Bipolar disorder is sometimes self-treated with cannabis since conventional treatments are often unsatisfactory and a number of case reports have been described where it has been used either instead of conventional drugs or as an adjunct, enabling, for example, a reduction in the dose of lithium.[61] However, again, conflicting reports exist.[62,63]

Acute psychosis has been cited as a consequence of cannabis use, but an examination of 10 000 psychiatric hospital admissions found no evidence that use of cannabis induced psychosis in previously asymptomatic individuals.[63] In patients with existing psychiatric disorders the situation may be different and cannabis use may exacerbate psychotic symptoms.[64] It has been suggested that the etiology of schizophrenia may include an imbalance in endogenous cannabinoid signalling, since cerebrospinal levels of anandamide and palmitylethanolamide were found to be elevated in patients with schizophrenia.[65] In addition, healthy volunteers intoxicated with THC showed similar results in neuropsychological tests (3-dimensional inversion illusion) to those found in patients with schizophrenia.[66] CBD showed a pharmacological profile similar in some respects to atypical antipsychotics in an animal model predictive of antipsychotic behaviour, for example, by reducing the occurrence of stereotyped biting induced by apomorphine but, in contrast to haloperidol, without catalepsy even at high doses.[67] This finding has been supported by a case report.[68]

These results emphasise the difference between the constituents of cannabis and illustrate once again the potential modifying effect of CBD towards THC. Much more work needs to be done before the therapeutic relevance of cannabinoids in psychiatric illness can be assessed.

2.2 Cardiovascular Conditions

Cannabis has cardiovascular effects,[1,59] but apart from a possible application for treating migraine,[46,47] they are usually considered to be adverse effects and include tachycardia and hypotension.[1,4] A peripheral endocannabinoid system is thought to be activated in septic and haemorrhagic shock, contributing to the associated hypotension,[69] and again cannabidiol is implicated[1,70] suggesting that at least some of the cardiovascular actions are independent of psychoactivity. The therapeutic opportunities opened up by the these properties of the endocannabinoids and the possible role of anandamide in regulating blood pressure[19] are still some way from clinical use, but may result in the development of antihypertensives with a novel mode of action.

2.3 Glaucoma

In 1971, it was observed that smoking cannabis reduced intra-ocular pressure (IOP) by about 45%.[71] This finding has been confirmed by others and shown to be due to THC, with CBD being inactive.[72] The mechanism of action is thought to involve prostaglandins, but not carbonic anhydrase.[73] Topically applied THC caused significant hypotension and reduced IOP in the control eye of test individuals in an unconfirmed study,[74] so at present, the situation is that using cannabinoids to treat glaucoma would cause unacceptable adverse effects unless suitable non-psychoactive derivatives are developed.[75]

2.4 Antiemetic Effects

This is the most widely used indication, mainly for dronabinol (THC) and nabilone. Studies in patients with CIE have mainly been carried out using orally administered isolated cannabinoids rather than smoking cannabis herb, which would be unlikely to appeal to most patients in the aftermath of cancer chemotherapy. However, limited evidence suggests that those patients who do try this route find smoking to be more effective than oral ingestion.[4,76] The evidence for the use of cannabinoids

for CIE is clear, particularly where other therapies have failed.[77,78] They are more effective than prochlorperazine alone, and a combination of cannabinoids with prochlorperazine is estimated to be as effective as high-dose metoclopramide and dexamethasone, with patients preferring the prochlorperazine-cannabinoid combination.[79] Δ^8-THC was used at high doses (18 mg/m^2) as an antiemetic to treat 8 children with various haematological cancers. Vomiting was completely suppressed and adverse effects were minimal. Although Δ^8-THC is less psychotropic than Δ^9-THC, this seems to confirm that children can tolerate the effects of cannabinoids fairly well.[80] The effect of cannabinoids on other types of nausea and vomiting are, in general, less pronounced.[4]

2.5 Appetite Stimulation

Smoking cannabis is known to stimulate the appetite,[2,5] and this effect is proposed as a basis for the use of cannabis in wasting diseases and anorexia particularly for patients with AIDS. Several clinical studies support this, with the effects of dronabinol 2.5mg twice daily on bodyweight, appetite, nausea and mood being examined. In all cases it was concluded that it improved appetite and mood, decreased nausea and stabilised bodyweight, and could therefore increase the quality of life in patients infected with HIV.[81-83] In the largest of these studies, a multicentre double-blind, placebo-controlled study, efficacy was measurable in 88 of the 139 patients.[83] Adverse effects tended to be mild to moderate, with dizziness and euphoria being the most common.

2.6 Asthma

THC is a bronchodilator when given orally and as an aerosol,[84,85] and the cannabinoids have a long duration of action.[3] Anecdotal evidence suggests cannabis herb itself may be useful for the treatment of asthma but smoking is hardly acceptable in lung disease, and other constituents of cannabis smoke can paradoxically cause bronchoconstriction by irritation. Therefore, the role of the cannabinoids in asthma remains limited at present.

3. Problems with Using Cannabinoids

With a herbal extract there are real problems with measuring the contribution made by each constituent of a mixture. As well as the cannabinoids, there are other plant constituents, such as flavonoids and monoterpenes, to mention only 2 (large) groups. These could have a modifying effect, either pharmacologically or as a result of altering the pharmacokinetic parameters of the others, and mistakes have been made in using unstandardised extracts for clinical testing. As an illustration of the futility of this approach, it could be compared with using an uncharacterised mixture of synthetic drugs, where all of the components could not be verified, and even the dose was an unknown quantity.

3.1 The Placebo Effect

It is difficult to measure the placebo effect of smoking cannabis, as it is almost impossible to 'blind' patients to what they are smoking. A recent study was carried out where the information individuals were given was manipulated so that although both groups took the same preparations, the information they were given differed.[86] The 'informed' patients, who expected to receive either THC or placebo, reported more pleasurable responses for orally-administered THC, but also more pronounced tachycardia, compared with the 'uninformed' group of patients, who did not know what to expect. The placebo response was high, and differing expectancies influenced the outcome for both subjective and physiological responses.

3.2 Dose and Route of Administration

The bioavailability of cannabis preparations has not been well investigated. Cannabis is usually smoked, simply because this is the quickest and most reproducible method of obtaining an effect. Where subjective assessment of the effect is needed, smoking enables some form of self-titration of dose. The safety of cannabis and the cannabinoids is fairly good but for therapeutic use most patients prefer to retain some alertness, requiring a fairly narrow dosage range above which drowsiness and

lack of concentration and coordination occur, which would be unacceptable. Smoking carries its own dangers, although for some these may be tolerable if relief of severe chronic pain is achieved. During smoking, the acids are decarboxylated to the active free cannabinoids, which may explain why giving cannabis orally is less effective than when smoked. This is well known by cannabis users and has now been demonstrated clinically.[31] Pharmacokinetic differences between orally administered and inhaled THC, including its active metabolites, are not well investigated.[87] Parameters such as absorption, time to maximum plasma concentration and duration of clinical effect will need to be clarified, and it would be advisable to eliminate the 'high' obtained during smoking, to avoid any dependency problems.

3.3 Metabolism

THC enters the bloodstream rapidly after smoking because of its lipophilicity, and is absorbed into fat tissue, where it may be detected for over 4 weeks.[88] It is released back into the bloodstream gradually and this is a rate-limiting step in its metabolism.[89] THC is fairly quickly converted to 11-hydroxy-THC, a metabolite which is equipotent with THC itself; to 11-nor-9-carboxy-Δ^9 THC, which is inactive; and to other cannabinoids, primarily by cytochrome P450 enzymes.[87] The relatively slow elimination from the body of the cannabinoids has implications regarding safety for cognitive tasks, especially relating to driving and operating machinery, if therapeutic use of cannabinoids is to be introduced.

3.4 Adverse Effects and Interactions

Cannabis itself has a remarkably good safety profile, with a therapeutic index estimated at 40 000 : 1.[4] Adverse reactions to cannabis include panic or anxiety attacks, which are worse in the elderly and in women, and less likely in children. They are mainly due to THC and are lessened by the presence of CBD.[1,4,20] Undesirable cardiovascular effects include tachycardia and orthostatic hypotension.[4] Psychiatric disorders may be exacerbated if already present but are rarely induced if not,[62,64] and amotivational syndrome is common amongst long term cannabis users.[63] The problem of driving while taking cannabinoids is a cause for concern, and although driving impairment has been shown to be only moderate, the interaction with alcohol which impairs driving ability significantly[90] is more worrying. The 'hangover' effect seems to be reasonably weak fortunately.[91] Other problems attributed to cannabis, when used recreationally rather than medicinally, include gynaecomastia, impairment of fetal growth, and a reduction in fertility and immune function.[4] The possibility of dependency is an emotive and controversial issue, with the general consensus being that it is a psychological rather than physiological dependence.[92] An interaction with opioids has been postulated, in that cannabinoids may increase the synthesis or release of endogenous opioids, and may up-regulate opioid gene expression in pain-regulated brain and spinal cord areas and regions which regulate motor activity and pituitary secretion.[93]

4. Future Research and Applications

Future clinical development will focus on either the use of the whole cannabis extract or the production of individual cannabinoids. With the plant extract, an advantage is that anecdotal evidence exists to justify further investigation. Several components of the mixture are known to be active and in some cases the combination gives a superior result to that of a single compound. However, natural materials are highly variable, because of genetic factors and growing and processing conditions, and multiple components need to be standardised to ensure reproducible effects and pharmacokinetics which are more complicated with a mixture. Microbial contamination may need to be assessed and dealt with. Pure compounds do not have these particular disadvantages but as novel entities their properties may be completely different, and need to be investigated more thoroughly before entering phase I trials. Both lines of research are valid, and after many years of being dismissed, perhaps this fascinating but maligned plant will fulfil its potential.

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